PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

DOCETAXEL 20 mg/mL and 80 mg/4 mL FRESENIUS

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

DOCETAXEL 20 mg/mL FRESENIUS concentrate for solution for infusion

DOCETAXEL 80 mg/4 mL FRESENIUS concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 20 mg docetaxel anhydrous.

DOCETAXEL 20 mg/mL FRESENIUS

One vial of 1 mL of concentrate contains 20 mg of docetaxel.

Excipient with known effect:

Each vial of concentrate contains 39,5 % *m/v* of ethanol anhydrous.

Sugar free.

DOCETAXEL 80 mg/4 mL FRESENIUS

One vial of 4 mL of concentrate contains 80 mg of docetaxel.

Excipient with known effect:

Each vial of concentrate contains 39,5 % *m/v* ethanol anhydrous.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Sterile, clear, colourless to pale yellow solution available in single dose vials for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- **Breast cancer:**

DOCETAXEL FRESENIUS, in combination with doxorubicin, is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.

DOCETAXEL FRESENIUS monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer, after failure of cytotoxic therapy.

DOCETAXEL FRESENIUS, in combination with capecitabine, is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

- **Non-small cell lung cancer:**

DOCETAXEL FRESENIUS, in combination with cisplatin, is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, who have not previously received chemotherapy for this condition.

DOCETAXEL FRESENIUS is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, even after failure of platinum-based chemotherapy.

- **Ovarian cancer:**

DOCETAXEL FRESENIUS is indicated, after failure of first-line or subsequent chemotherapy, for treatment of metastatic carcinoma of the ovary.

- **Prostate cancer:**

DOCETAXEL FRESENIUS, in combination with prednisone or prednisolone, is indicated for the treatment of patients with androgen-independent (hormone refractory) metastatic prostate cancer.

4.2 Posology and method of administration

DOCETAXEL FRESENIUS should be administered by intravenous infusion only.

Posology

A premedication consisting of a corticosteroid (see below for prostate cancer), such as oral dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to **DOCETAXEL FRESENIUS** administration, unless contraindicated, can be used. For prostate cancer, given the concurrent use of prednisone or prednisolone, the recommended premedication regimen is oral dexamethasone 8 mg administered 12 hours, 3 hours and 1 hour before the **DOCETAXEL FRESENIUS** infusion.

- **Breast cancer:**

In first-line treatment, **DOCETAXEL FRESENIUS** 75 mg/m^2 is administered in combination therapy with doxorubicin (50 mg/m^2).
For second-line monotherapy for previously treated patients, the recommended dose of **DOCETAXEL FRESENIUS** therapy is 100 mg/m^2.

In combination with capecitabine, the recommended dose of **DOCETAXEL FRESENIUS** is 75 mg/m^2 every three weeks, combined with capecitabine at 1 250 mg/m^2 orally twice daily (within 30 minutes after a meal) for 2 weeks followed by a 1-week rest period. For capecitabine dose calculation according to body surface area, see capecitabine manufacturer's professional information.

- **Non-small cell lung cancer:**

In combination therapy (chemotherapy-naïve patients):

The recommended dose regimen is **DOCETAXEL FRESENIUS** 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30 – 60 minutes.

In monotherapy (for previously treated patients):

The recommended dose of **DOCETAXEL FRESENIUS** therapy is 100 mg/m^2 as a single medicine.

- **Ovarian cancer:**

The recommended dose of **DOCETAXEL FRESENIUS** therapy is 100 mg/m^2.

- **Prostate cancer:**

The recommended dose of **DOCETAXEL FRESENIUS** is 75 mg/m^2. Prednisone or prednisolone 5 mg orally twice daily is administered continuously.

Patients should be observed closely, especially during the first and second infusion of **DOCETAXEL FRESENIUS**, because of the risk of hypersensitivity reactions.

Dosage adjustments during treatment:

General:

ONLY the medical practitioner can modify the schedule of administration.

DOCETAXEL FRESENIUS should be administered when the neutrophil count is ≥ 1 500 cells/mm^3. Patients who experienced either febrile neutropenia, neutrophil count < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms during **DOCETAXEL FRESENIUS** therapy, should have the dose of **DOCETAXEL FRESENIUS** reduced during the subsequent cycle, from 100 mg/m^2 to 75 mg/m^2 and/or from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, treatment should be discontinued.

Combination therapy with DOCETAXEL FRESENIUS for non-small cell lung cancer:

For patients who were dosed initially at **DOCETAXEL FRESENIUS** 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy was < 25 000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haematological toxicities, the **DOCETAXEL FRESENIUS** dose in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dose adjustments, see the manufacturer's professional information.

Combination with therapy DOCETAXEL FRESENIUS for breast cancer:

Patients who receive adjuvant therapy for breast cancer and who experience febrile neutropenia should receive granulocyte colony-stimulating factor (G-CSF) in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their **DOCETAXEL FRESENIUS** dose reduced to 60 mg/m^2. If G-CSF is not used, the **DOCETAXEL FRESENIUS** dose should be reduced from 75 mg/m^2 to 60 mg/m^2.

For capecitabine dose modifications when combined with **DOCETAXEL FRESENIUS**, see capecitabine manufacturer's professional information.

For patients developing the first appearance of grade 2 toxicity which persists at the time of the next **DOCETAXEL FRESENIUS**/ capecitabine treatment, delay treatment until resolved to grade 0 – 1, and resume at 100 % of the original dose. For patients developing the second appearance of grade 2 toxicity, or the first appearance of grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to grade 0 – 1, then resume treatment with **DOCETAXEL FRESENIUS** 55 mg/m^2. For any subsequent appearances of toxicities, or any grade 4 toxicities, discontinue the **DOCETAXEL FRESENIUS** dose.

For **DOCETAXEL FRESENIUS** dose modifications due to hepatic impairment, see section 4.4 and ***Special populations*** below.

Special populations:

Patients with hepatic impairment:

Patients with bilirubin > ULN (upper limit of normal) should generally not receive **DOCETAXEL FRESENIUS**. Also, patients with AST (aspartate aminotransferase) and/or ALT (alanine transaminase) > 1,5 x ULN concomitant with alkaline phosphatase > 2,5 x ULN should generally not receive **DOCETAXEL FRESENIUS**.

Paediatric population:

The safety and effectiveness of **DOCETAXEL FRESENIUS** in children have not been established (see section 4.3).

Elderly:

Based on a population pharmacokinetic analysis, there are no special instructions for use in the elderly.

For capecitabine dose reduction when combined with **DOCETAXEL FRESENIUS**, see capecitabine manufacturer's professional information.

Method of administration

Intravenous infusion.

For instructions on preparation and administration of **DOCETAXEL FRESENIUS**, see section 6.6.

4.3 Contraindications

- Hypersensitivity to docetaxel or to any of the excipients listed in section 6.1.

- Patients with baseline neutrophil count of < 1 500 cells/mm^3.
- Patients with severe liver impairment (see sections 4.2 and 4.4).
- Contraindications for other medicine also apply, when combined with **DOCETAXEL FRESENIUS**.
- Pregnancy and lactation, as **DOCETAXEL FRESENIUS** is teratogenic in animals (see section 4.6).
- The safe use of **DOCETAXEL FRESENIUS** in children has not been established.

4.4 Special warnings and precautions for use

DOCETAXEL FRESENIUS should be administered under the supervision of a qualified medical practitioner experienced in the use of antineoplastic medicines.
Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.
The incidence of treatment-related mortality associated with **DOCETAXEL FRESENIUS** therapy is increased in patients with abnormal liver function and in patients receiving higher doses.
DOCETAXEL FRESENIUS should generally not be given to patients with serum bilirubin levels > upper limit of normal (ULN), or to patients with AST and/or ALT > 1,5 x ULN concomitant with alkaline phosphatase levels > 2,5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminases concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity and toxic death.

Patients with isolated elevations of transaminase > 1,5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, AST or ALT and alkaline phosphatase values should be obtained prior to each cycle of **DOCETAXEL FRESENIUS** therapy and reviewed by the treating medical practitioner.

DOCETAXEL FRESENIUS therapy should not be given to patients with neutrophil counts of < 1 500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving **DOCETAXEL FRESENIUS**.

Severe hypersensitivity reactions characterised by hypotension and/or bronchospasm or generalised rash/erythema occurred in 2,2 % (2/92) of patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of **DOCETAXEL FRESENIUS** were reported in five patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy.

DOCETAXEL FRESENIUS must not be given to patients who have a history of severe hypersensitivity reactions to **DOCETAXEL FRESENIUS** or to other medicines formulated with polysorbate 80.
Severe fluid retention occurred in 6,5 % (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterised by one or more of the following events: poorly tolerated peripheral oedema, generalised oedema, pleural effusion requiring urgent drainage, dyspnoea at rest, cardiac tamponade or pronounced abdominal distension (due to ascites).

For breast and non-small cell lung cancers, premedication consisting of an oral corticosteroid (see below for prostate cancer), such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to **DOCETAXEL FRESENIUS** administration, unless contraindicated, may reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. For prostate cancer, the premedication is oral

dexamethasone 8 mg administered 12 hours, 3 hours and 1 hour before the **DOCETAXEL FRESENIUS** infusion (see section 4.2).

Haematology

Neutropenia is the most frequent adverse reaction of docetaxel. Neutrophil nadirs occurred at a median of 7 days but this interval may be shorter in heavily pre-treated patients. Frequent monitoring of complete blood counts should be conducted on all patients receiving **DOCETAXEL FRESENIUS**. Patients should be retreated with **DOCETAXEL FRESENIUS** when neutrophils recover to a level ≥ 1 500 cells/mm^3 (see section 4.2).

In the case of severe neutropenia (< 500 cells/mm^3 for seven days or more) during a course of **DOCETAXEL FRESENIUS** therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended (see section 4.2).
In patients treated with **DOCETAXEL FRESENIUS** in combination with cisplatin and 5-fluorouracil (TCF), febrile neutropenia and neutropenic infection occurred at lower rates when patients received prophylactic G-CSF. Patients treated with TCF should receive prophylactic G-CSF to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TCF should be closely monitored (see sections 4.2 and 4.8).

In patients treated with **DOCETAXEL FRESENIUS** in combination with doxorubicin and cyclophosphamide (TAC), febrile neutropenia and/or neutropenic infection occurred at lower rates when patients received primary G-CSF prophylaxis. Primary G-CSF prophylaxis should be considered in patients who receive adjuvant therapy with TAC for breast cancer to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TAC should be closely monitored (see sections 4.2 and 4.8).

Gastrointestinal reactions

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Although majority of cases occurred during the first or second cycle of docetaxel containing regimen, enterocolitis could develop at any time, and could lead to death as early as on the first day of onset. Patients should be closely monitored for early manifestations of serious gastrointestinal toxicity (see sections 4.2, 4.4 ***Haematology*** and 4.8).

Hypersensitivity reactions

Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of **DOCETAXEL FRESENIUS**, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of **DOCETAXEL FRESENIUS** and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with **DOCETAXEL FRESENIUS**. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop a hypersensitivity reaction to docetaxel, including a more severe hypersensitivity reaction. These patients should be closely monitored during initiation of **DOCETAXEL FRESENIUS** therapy.

Cutaneous reactions

Localised skin erythema of the extremities (palms of the hands and soles of the feet) with oedema followed by desquamation has been observed. Severe symptoms such as eruptions followed by desquamation which lead to interruption or discontinuation of **DOCETAXEL FRESENIUS** treatment were reported (see section 4.2).

Fluid retention

Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely.

Respiratory disorders

Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported and may be associated with fatal outcome. Cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated and appropriately treated. Interruption of **DOCETAXEL FRESENIUS** therapy is recommended until a diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming **DOCETAXEL FRESENIUS** treatment must be carefully evaluated.

Patients with liver impairment

In patients treated with **DOCETAXEL FRESENIUS** at 100 mg/m^2 as single medicine who have serum transaminase levels (ALT and/or AST) greater than 1,5 times the ULN concurrent with serum alkaline phosphatase levels greater than 2,5 times the ULN, there is a higher risk of developing severe adverse reactions such as toxic deaths including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of **DOCETAXEL FRESENIUS** in those patients with elevated liver function tests (LFTs) is 75 mg/m^2 and LFTs should be measured at baseline and before each cycle (see section 4.2).

For patients with serum bilirubin levels > ULN and/or ALT and AST > 3,5 times the ULN concurrent with serum alkaline phosphatase levels > 6 times the ULN, no dose reduction can be recommended, and **DOCETAXEL FRESENIUS** should not be used unless strictly indicated.

In combination with cisplatin and 5-fluorouracil for the treatment of patients with gastric adenocarcinoma, the pivotal clinical study excluded patients with ALT and/or AST > 1,5 x ULN associated with alkaline phosphatase > 2,5 x ULN, and bilirubin > 1 x ULN; for these patients, no dose reductions can be recommended and **DOCETAXEL FRESENIUS** should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by docetaxel, as in **DOCETAXEL FRESENIUS** in combination in the other indications.

Patients with renal impairment

There are no data available in patients with severely impaired renal function treated with docetaxel, as in **DOCETAXEL FRESENIUS**.

Nervous system

The development of severe peripheral neurotoxicity requires a reduction of dose (see section 4.2).

Cardiac toxicity

Heart failure has been observed in patients receiving **DOCETAXEL FRESENIUS** in combination with trastuzumab, particularly following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death (see section 4.8).
When patients are candidates for treatment with docetaxel in combination with trastuzumab, they should undergo baseline cardiac assessment.
Cardiac function should be further monitored during treatment (e.g. every three months) to help identify patients who may develop cardiac dysfunction. For more details see professional information leaflet of trastuzumab.
Ventricular dysrhythmia including ventricular tachycardia (sometimes fatal) has been reported in patients treated with **DOCETAXEL FRESENIUS** in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide (see section 4.8). Baseline cardiac assessment is recommended.

Eye disorders

Cystoid macular oedema (CMO) has been reported in patients treated with **DOCETAXEL FRESENIUS**. Patients with impaired vision should undergo a prompt and complete ophthalmological examination. In case CMO is diagnosed, docetaxel treatment should be discontinued, and appropriate treatment initiated (see section 4.8).

Second primary malignancies

Second primary malignancies have been reported when docetaxel was given in combination with anticancer treatments known to be associated with second primary malignancies. Second primary malignancies (including acute myeloid leukaemia, myelodysplastic syndrome and non-Hodgkin lymphoma) may occur several months or years after docetaxel-containing therapy. Patients should be monitored for second primary malignancies (see section 4.8).

Others

Contraceptive measures must be taken by both men and women during treatment and for men at least 6 months after cessation of therapy (see section 4.6).

The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided (see section 4.5).

Additional cautions for use in adjuvant treatment of breast cancer

Complicated neutropenia

For patients who experience complicated neutropenia (prolonged neutropenia, febrile neutropenia or infection), G-CSF and dose reduction should be considered (see section 4.2).

Gastrointestinal reactions

Symptoms such as early abdominal pain and tenderness, fever, diarrhoea, with or without

neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly.

Congestive heart failure (CHF)

Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow-up period. In patients treated with the TAC regimen for node positive breast cancer, the risk of CHF has been shown to be higher during the first year after treatment (see sections 4.8 and 5.1).

Patients with 4+ nodes

As the benefit observed in patient with 4+ nodes was not statistically significant on disease-free survival (DFS) and overall survival (OS), the positive benefit/risk ratio for TAC in patients with 4+ nodes was not fully demonstrated at the final analysis (see section 5.1).

Elderly

There are limited data available in patients > 70 years of age on docetaxel use in combination with doxorubicin and cyclophosphamide.

Of the 333 patients treated with docetaxel every three weeks in a prostate cancer study, 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with docetaxel every three weeks, the incidence of related nail changes occurred at a rate ≥ 10 % higher in patients who were 65 years of age or greater compared to younger patients. The incidence of related fever, diarrhoea, anorexia, and peripheral oedema occurred at rates ≥ 10 % higher in patients who were 75 years of age or greater versus less than 65 years.
Among the 300 (221 patients in the phase III part of the study and 79 patients in the phase II part) patients treated with docetaxel in combination with cisplatin and 5-fluorouracil in the gastric cancer study, 74 were 65 years of age or older and 4 patients were 75 years of age or older.

The incidence of serious adverse events was higher in older people compared to younger patients. The incidence of the following adverse events (all grades): lethargy, stomatitis, neutropenic infection occurred at rates ≥ 10 % higher in patients who were 65 years of age or older compared to younger patients.

Elderly patients treated with TCF should be closely monitored.

DOCETAXEL FRESENIUS contains 50,0 % *v/v* (39,5 % *m/v*) ethanol (ethyl alcohol), i.e. 0,5 mL (395 mg) per mL, equivalent to 10 mL beer or 4 mL wine.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease or epilepsy.

4.5 Interaction with other medicines and other forms of interaction

The amount of alcohol in **DOCETAXEL FRESENIUS** may alter the effects of other medicines.

In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A (CYP3A) such as ciclosporin, ketoconazole and erythromycin. As a result, caution should be exercised when treating patients with these medicines as concomitant therapy, since there is a potential for a significant interaction.

In case of combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, as a result of reduced metabolism. If the concomitant use of a strong CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor (see section 4.4). In a pharmacokinetic study with 7 patients, the co-administration of docetaxel with the strong CYP3A4 inhibitor ketoconazole leads to a significant decrease in docetaxel clearance by 49 %.

Docetaxel pharmacokinetics in the presence of prednisone was studied in patients with metastatic prostate cancer. Docetaxel is metabolised by CYP3A4 and prednisone is known to induce CYP3A4. No statistically significant effect of prednisone on the pharmacokinetics of docetaxel was observed. Docetaxel is highly protein bound (> 95 %). Although the possible *in vivo* interaction of docetaxel with concomitantly administered medicine has not been investigated formally, *in vitro* interactions with tightly protein-bound medicines such as erythromycin, diphenhydramine, propranolol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect protein binding of docetaxel. In addition, dexamethasone did not affect protein binding of docetaxel. Docetaxel did not influence the binding of digoxin.

The pharmacokinetics of docetaxel, doxorubicin and cyclophosphamide were not influenced by their co-administration. Limited data from a single uncontrolled study were suggestive of an interaction between docetaxel and carboplatin. When combined to docetaxel, the clearance of carboplatin was about 50 % higher than values previously reported for carboplatin monotherapy.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing age receiving **DOCETAXEL FRESENIUS** should be advised to avoid becoming pregnant, and to inform the treating medical practitioner immediately should this occur. An effective method of contraception should be used during treatment.

Pregnancy

There is no information on the use of **DOCETAXEL FRESENIUS** in pregnant women. Docetaxel has been shown to be both embryotoxic and fetotoxic in rabbits and rats, and to reduce fertility in rats (see section 5.3). As with other cytotoxic medicines, docetaxel may cause fetal harm when administered to pregnant women. Therefore, **DOCETAXEL FRESENIUS** must not be used during pregnancy (see section 4.3).

Breastfeeding

Docetaxel is a lipophilic substance, but it is not known whether it is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breastfeeding must be discontinued for the duration of docetaxel therapy (see section 4.3).

Fertility

In non-clinical studies, docetaxel has genotoxic effects and may alter male fertility (see section 5.3). Therefore, men being treated with **DOCETAXEL FRESENIUS** are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

4.7 Effects on ability to drive and use machines

The amount of alcohol in **DOCETAXEL FRESENIUS** and the side effects of **DOCETAXEL FRESENIUS** may impair the ability to drive a vehicle or use machines (see sections 4.4 and 4.8). Therefore, patients should be warned of the potential impact of the amount of alcohol and the side effects of **DOCETAXEL FRESENIUS** on the ability to drive a vehicle or use machines, and be advised not to drive a vehicle or use machines if they experience these side effects during treatment.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Frequent: Bone marrow suppression and other haematological adverse reactions include neutropenia, febrile neutropenia, thrombocytopenia, anaemia and infections. Neutropenia is reversible and not cumulative. The median time to nadir is 7 days and the median duration of severe neutropenia (< 500 cells/mm^3) is 7 days. Fever in absence of infection, has been reported in patients with non-small cell lung cancer.

Less frequent: Bleeding episodes have occurred and were rarely associated with severe thrombocytopenia (< 50 000 cells/mm^3).

Immune system disorders:

Frequent: Hypersensitivity reactions may occur, usually within a few minutes following the start of the infusion of **DOCETAXEL FRESENIUS** and are mostly mild to moderate.
Symptoms are flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills.
Severe reactions characterised by hypotension and/or bronchospasm or generalised rash/erythema, requiring therapeutic intervention, may occur. These may resolve after discontinuation of the infusion and institution of appropriate therapy.

Metabolism and nutrition disorders:

Less frequent: Fluid accumulation: Peripheral oedema, pleural effusion, pericardial effusion, ascites, increased capillary permeability and weight gain, have been reported. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more after 4 cycles or a cumulative dose ≥ 400 mg/m^2. Fluid retention is cumulative in incidence and severity.
The onset of moderate and severe retention is delayed in patients with premedication, compared with patients without premedication. However, it has been reported in some patients during the early courses of therapy. The median time to fluid retention reversibility is 16,4 weeks (range 0 to 42 weeks) in patients receiving the recommended premedication. Fluid retention has not been accompanied by acute episodes of oliguria or hypotension.
Fluid retention has been less frequently reported in patients receiving the recommended premedication compared with patients without premedication. Dehydration and pulmonary oedema have been reported.

Nervous system disorders:

Frequent: Neurosensory signs characterised by paraesthesia, dysaesthesia or pain, including burning, may occur.

Neuromotor events, mainly characterised by weakness, may occur.

Cases of convulsion or transient loss of consciousness have been observed with **DOCETAXEL FRESENIUS** administration. These reactions may appear during the infusion of **DOCETAXEL FRESENIUS**.

Eye disorders:

Less frequent: Lacrimation, with or without conjunctivitis, individual cases of lacrimal duct obstruction resulting in excessive tearing, transient visual disturbances (flashes, flashing lights, scotomata), typically occurring during medicine infusion and in association with hypersensitivity reactions.

Cardiovascular system disorders:

Less frequent: Venous thromboembolic events, myocardial infarction, hypertension.

Other adverse events include left ventricular dysfunction, unstable angina, dysrhythmia, sinus tachycardia, atrial flutter or paroxysmal atrial tachycardia and hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea may occur and is associated with acute hypersensitivity reactions, respiratory infections and cancerous lung involvement.

Less frequent: Cough and epistaxis.

Acute respiratory distress syndrome, interstitial pneumonia, pulmonary fibrosis and radiation recall phenomena have been reported.

Gastrointestinal system disorders:

Frequent: Gastrointestinal effects, such as nausea, vomiting, diarrhoea and abdominal pain, constipation, stomatitis, oesophagitis and taste perversion.

Gastrointestinal bleeding, anorexia.

Occurrences of dehydration as a consequence of gastrointestinal events, gastrointestinal perforation, ischaemic colitis, colitis and neutropenic enterocolitis.

Less frequent: Ileus and intestinal obstruction.

Hepatobiliary system disorders:

Less frequent: Increases in serum levels of AST, ALT, bilirubin and alkaline phosphatase greater than 2,5 times ULN, hepatitis.

Skin and subcutaneous tissue disorders:

Frequent: Reversible cutaneous reactions.

The cutaneous reactions are characterised by a rash, including localised eruptions mainly on the feet and hands, but also on the arms, face or thorax, and frequently associated with pruritus.

Eruptions generally occurred within one week after the **DOCETAXEL FRESENIUS** infusion.

Nail disorders may occur. These are characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis.

Less frequent: Severe symptoms, such as eruptions followed by desquamation, may lead to interruption or discontinuation of **DOCETAXEL FRESENIUS** treatment.

Bullous eruptions, such as erythema multiforme or Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders:

Frequent: Arthralgia and myalgia.

General disorders and administration site conditions:

Frequent: Infusion site reactions are generally mild and consist of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein.

Generalised or localised pain may occur, including chest pain without any cardiac or respiratory involvement.

Other side effects include alopecia and asthenia.

Combination therapy with DOCETAXEL FRESENIUS in the adjuvant treatment of breast cancer:

Clinically important treatment-related adverse events in patients receiving docetaxel, as in DOCETAXEL FRESENIUS, in combination with doxorubicin and cyclophosphamide:

Infections and infestations:

Frequent: Infection.

Blood and lymphatic system disorders:

Frequent: Anaemia, neutropenia, fever in absence of infection, thrombocytopenia, febrile neutropenia, neutropenic infection.

Immune system disorders:

Frequent: Hypersensitivity reactions.

Metabolism and nutrition disorders:

Frequent: Peripheral oedema, weight gain or loss.

Less frequent: Lymph oedema.

Nervous system disorders:

Frequent: Sensory neuropathy, syncope.

Less frequent: Neuro-cortical adverse events, motor neuropathy and neuro-cerebellar adverse events.

Eye disorders:

Less frequent: Lacrimation disorder, conjunctivitis.

Cardiac disorders:

Less frequent: Cardiac dysrhythmias.

Vascular disorders:

Frequent: Vasodilatation.

Less frequent: Hypotension, phlebitis.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Cough.

Gastrointestinal disorders:

Frequent: Anorexia, nausea, stomatitis, vomiting, diarrhoea, taste perversion, constipation.

Less frequent: Abdominal pain.

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, skin toxicity, nail disorders.

Musculoskeletal and connective tissue disorders:

Frequent: Myalgia, arthralgia.

Reproductive system and breast disorders:

Frequent: Amenorrhoea.

General disorders and administration site conditions:

Frequent: Asthenia.

Combination therapy with DOCETAXEL FRESENIUS and capecitabine for breast cancer:

Summary of at least remotely related adverse events reported in ≥ 5 % of patients treated with docetaxel, as in DOCETAXEL FRESENIUS, and capecitabine in combination:

Infections and infestations:

Less frequent: Oral candidiasis.

Metabolism and nutrition disorders:

Less frequent: Dehydration, decreased weight.

Nervous system disorders:

Frequent: Paraesthesia.

Less frequent: Dizziness, headache, peripheral neuropathy.

Eye disorders:

Frequent: Increased lacrimation.

Vascular disorders:

Frequent: Lower limb oedema.

Respiratory, thoracic and mediastinal disorders:

Frequent: Sore throat.

Less frequent: Dyspnoea, cough, epistaxis.

Gastrointestinal disorders:

Frequent: Taste disturbance, anorexia, decreased appetite, stomatitis, diarrhoea, nausea, vomiting, constipation, abdominal pain, dyspepsia.

Less frequent: Upper abdominal pain, dry mouth.

Skin and subcutaneous tissue disorders:

Frequent: Hand-foot syndrome, alopecia, nail disorder.

Less frequent: Dermatitis, erythematous rash, nail discolouration, onycholysis.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia, arthralgia.

Less frequent: Back pain.

General disorders and administration site conditions:

Frequent: Asthenia, pyrexia, fatigue, weakness.

Less frequent: Pain in limb, lethargy, pain.

Investigations:

Frequent: Neutropenia, anaemia.

Less frequent: Thrombocytopenia, hyperbilirubinaemia.

Combination therapy with DOCETAXEL FRESENIUS in prostate cancer patients:

Clinically important treatment-related adverse events in patients with prostate cancer who received docetaxel, as in DOCETAXEL FRESENIUS, in combination with prednisone or prednisolone:

Infection and infestations:

Frequent: Infection.

Blood and lymphatic system disorders:

Frequent: Anaemia, neutropenia.

Less frequent: Thrombocytopenia, febrile neutropenia.

Immune system disorders:

Less frequent: Allergic reactions.

Metabolism and nutrition disorders:

Frequent: Fluid retention.

Nervous system disorders:

Frequent: Sensory neuropathy, motor neuropathy.

Eye disorders:

Less frequent: Tearing.

Cardiac disorders:

Less frequent: Left ventricular dysfunction.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Epistaxis, cough, dyspnoea.

Gastrointestinal disorders:

Frequent: Nausea, diarrhoea, stomatitis/pharyngitis, taste disturbance, vomiting, anorexia.

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, nail changes.

Less frequent: Rash/desquamation.

Musculoskeletal and connective tissue disorders:

Less frequent: Myalgia, arthralgia.

General disorders and administration site conditions:

Frequent: Fatigue.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **DOCETAXEL FRESENIUS** is important. It allows continued monitoring of the benefit/risk balance of **DOCETAXEL FRESENIUS**. Health care providers are asked to report any suspected adverse reactions via the **6.04 Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There were a few reports of overdose. There is no known antidote for docetaxel overdose. In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. In cases of overdose, exacerbation of adverse events may be expected. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity, cutaneous reactions and mucositis.

Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 26 Cytostatic agents.

Pharmacotherapeutic group: Antineoplastic agents, plant alkaloids and other natural products, taxanes, ATC Code: L01CD02

5.1 Pharmacodynamic properties

Pharmacodynamic properties:

Docetaxel is an antineoplastic medicine which acts by promoting the assembly of tubulin into stable

microtubules and by inhibiting their disassembly, which leads to a marked decrease in free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments.
Docetaxel has been shown *in vitro* to disrupt the microtubular network in cells, which is essential for vital mitotic and interphase cellular functions. Docetaxel achieves high intracellular concentrations with a long cell residence time. In addition, docetaxel was found to be active on some, but not all, cell lines over-expressing the paraglycoprotein which is encoded by the multidrug resistance gene. *In vivo,* docetaxel is schedule-independent.

5.2 Pharmacokinetic properties

The kinetic profile of docetaxel is dose-independent and consistent with a three compartment pharmacokinetic model with half-lives for the alpha, beta and gamma phases of 4 minutes, 36 minutes and 11,1 hours, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.
Following the administration of a 100 mg/m^2 dose given as a one-hour infusion, a mean peak plasma level of 3,7 µg/mL is obtained with a corresponding AUC of 4,6 h.µg/mL. Mean values for total body clearance and steady-state volume of distribution are 21 L/h/m^2 and 113 L, respectively. Docetaxel is more than 95 % bound to plasma proteins.
Faecal excretion is the main route of elimination of docetaxel and its metabolites. Faecal and urinary excretions account for about 75 % and 6 % of the dose, respectively. Only a minor fraction of the dose is excreted as the parent compound.
Based on *in vitro* studies, isoenzymes of the cytochrome P450-3A subfamily appear to be involved in docetaxel metabolism.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80

Ethanol anhydrous

Anhydrous citric acid (pH adjustment).

6.2 Incompatibilities

DOCETAXEL FRESENIUS must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial:

2 years.

After opening of the vial:

Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Once added to the infusion bag:

From a microbiological point of view, reconstitution/dilution must take place in controlled and aseptic conditions and **DOCETAXEL FRESENIUS** should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Once added as recommended into the infusion bag, the docetaxel infusion solution, if stored below 25 °C, is stable for 6 hours. It should be used within 6 hours (including the one hour infusion intravenous administration).

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2 °C to 8 °C.

6.4 Special precautions for storage

- Store at or below 25 °C.
- Store in the original package in order to protect from light.
- For storage conditions of the diluted **DOCETAXEL FRESENIUS**, see section 6.3.

6.5 Nature and contents of container

DOCETAXEL 20 mg/mL FRESENIUS

6 mL clear, colourless Type-I tubular, glass vial, closed with grey FluroTec rubber stopper and a green flip-off aluminium over seal, containing 1 mL of concentrate.

DOCETAXEL 80 mg/4 mL FRESENIUS

6 mL clear, colourless Type-I tubular, glass vial, closed with grey flurotec rubber stopper and a blue flip-off aluminium over seal, containing 4 mL of concentrate.

Pack size: Each box contains one vial.

6.6 Special precautions for disposal and other handling

- **DOCETAXEL FRESENIUS** is an antineoplastic medicine and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing the solution. The use of gloves is recommended.
- If **DOCETAXEL FRESENIUS** concentrate or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If **DOCETAXEL FRESENIUS** concentrate or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Preparation for the intravenous administration

Preparation of the infusion solution

- **DO NOT use other docetaxel medicine consisting of 2 vials (concentrate and solvent) with this product (DOCETAXEL 20 mg/mL FRESENIUS or DOCETAXEL 80 mg/4 mL FRESENIUS concentrate for solution for infusion, which contains only 1 vial).**
- **DOCETAXEL 20 mg/mL FRESENIUS or DOCETAXEL 80 mg/4 mL FRESENIUS concentrate for solution for infusion requires NO prior dilution with a solvent and is ready to add to the infusion solution.**
- Each vial is for single use and should be used immediately.
- If the vials are stored under refrigeration, allow the required number of boxes of **DOCETAXEL FRESENIUS** concentrate for solution for infusion to stand below 25 °C for 5 minutes before use. More than one vial of **DOCETAXEL FRESENIUS** concentrate for solution for infusion may be necessary to obtain the required dose for the patient. Aseptically withdraw the required amount of **DOCETAXEL FRESENIUS** concentrate for solution for infusion using a calibrated syringe.
- **In DOCETAXEL 20 mg/1 mL FRESENIUS or DOCETAXEL 80 mg/4 mL FRESENIUS vial the concentration of docetaxel is 20 mg per 1 mL.**
- The required volume of **DOCETAXEL FRESENIUS** concentrate for solution for infusion must be injected via a single injection (one shot) into a 250 mL infusion bag or bottle containing either 5 % glucose solution or sodium chloride 9 mg/mL (0,9 %) solution for infusion.
- If a dose greater than 190 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0,74 mg/mL docetaxel is not exceeded.
- Mix the infusion bag or bottle manually using a rocking motion.
- The infusion bag solution should be used within 6 hours below 25 °C including the one hour infusion to the patient.

- As with all parenteral products, **DOCETAXEL FRESENIUS** infusion solution should be visually inspected prior to use, and solutions containing a precipitate should be discarded.
- **DOCETAXEL FRESENIUS** infusion solution is supersaturated, therefore may crystallise over time. If crystals appear, the solution must no longer be used and must be discarded.
- Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House Extension 7

Midrand, Gauteng 1685

8. REGISTRATION NUMBERS

DOCETAXEL 20 mg/mL FRESENIUS: 48/26/0667

DOCETAXEL 80 mg/4 mL FRESENIUS: 48/26/0668

9. DATE OF FIRST AUTHORISATION

04 May 2021

10. DATE OF REVISION OF THE TEXT